Axillary arterial angiosarcoma in a nonfunctioning arteriovenous fistula limb of a patient undergoing hemodialysis: case report with literature review

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Abstract

A 54-year-old man was admitted to our hospital with a painful left axillary mass. He had a 27-year history of hemodialysis for end-stage kidney disease because of chronic glomerulonephritis. He had a right radial artery–cephalic vein arteriovenous fistula and left nonfunctioning arteriovenous fistula. Computed tomography imaging showed a left axillary arterial mass with peripheral hematoma and multiple lung tumors. On hospital day 3, he showed disturbances in consciousness as well as enlargement of the axillary mass and hematoma. We performed emergency surgery to resect the left axillary tumor. The patient was diagnosed with angiosarcoma upon histopathological examination of the resected specimen on hospital day 15. Because his condition was extremely poor, we provided supportive care to him, not chemotherapy. He expired on hospital day 25. Angiosarcoma remains a rare disease; however, this case highlights the importance of including angiosarcoma in the differential diagnosis for upper extremity pain in patients undergoing hemodialysis.

Keywords Angiosarcoma · Arteriovenous fistula · Axillary artery · Hemodialysis

Introduction

Angiosarcoma is a rare but highly aggressive cancer of the vascular system arising from endothelial tissue. It has strong metastatic potential. Angiosarcoma can occur in any tissue of the body but has a high predilection for the head and neck region [1]. Previous research has shown that angiosarcoma can arise in a nonfunctional arteriovenous fistula (AVF) in patients undergoing hemodialysis (HD) [2]. To our knowledge, there have been approximately 30 case reports

in the literature that have demonstrated the development of angiosarcoma at the site of a nonfunctional AVF. Although it is rare, angiosarcoma remains an important consideration in the differential diagnosis for upper extremity pain and paresthesias in end-stage kidney disease when there is a nonfunctioning AVF. We describe a patient who presented with a painful axillary tumor who was diagnosed with angiosarcoma.

Case report

A 54-year-old man was admitted to our hospital because of a painful left axillary mass. He had a 27-year history of HD for end-stage kidney disease secondary to chronic glomerulonephritis. He also had a history of ulcerative colitis for which he was taking corticosteroids. On presentation, his height was 161 cm and weight 46 kg. He was alert, with a blood pressure of 116/80 mmHg, heart rate of 68 beats per minute, and body temperature of 36.2 °C. He had a right radial artery–cephalic vein AVF. There were multiple surgical marks on the left upper limb. His right AVF was functional; however, his left previous AVF was nonfunctional.

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We palpated a painful mass in the left axilla; the left upper limb showed no ischemic signs at this point. Laboratory data of non-dialysis day on presentation are shown in Table 1. Briefly, the following results were obtained: white blood cell count (12,150/ μ L), serum albumin (2.9 g/dL), lactate dehydrogenase (255 U/L), blood urea nitrogen (73 mg/dL), creatinine (8.6 mg/dL) and serum C-reactive protein (CRP) (9.13 mg/dL). Contrast-enhanced computed tomography (CT) revealed a mass involving the left axillary artery (57 mm long $\times$ 42 mm wide in diastole) with peripheral hematoma and multiple lung tumors (Fig. 1a, b). With the patient's history, elevated inflammation status on laboratory data, and imaging evaluation, the differential diagnosis included an infected (bacterial) arterial aneurysm and septic pulmonary embolism, an infected (fungal) arterial aneurysm and mycosis, granulomatosis with polyangiitis, and malignant lymphoma with lung metastasis. Sepsis was a primary suspect because of the high risk of infection in patients undergoing HD; moreover, the elevated inflammation status also supported this possibility. However, he had

a negative blood culture, only one sign of systemic inflammatory response syndrome with white blood cell count $\geq 12,000$ mm³, and no signs of quick sequential organ failure assessment score (respiratory rate ≥ 22 /min, altered mentation, systolic blood pressure ≤ 100 mmHg) [3]; therefore, his presentation would be atypical for sepsis. The possibility of a (fungal) infected aneurysm and mycosis, including invasive pulmonary aspergillosis, was ruled out with a beta-D-glucan study below the cutoff value. Granulomatosis with polyangiitis and lung metastasis was ruled out by a study negative for proteinase-3 anti-neutrophil cytoplasmic antibody. Finally, he had a normal lactate dehydrogenase level, which is not typical in malignant lymphoma. The risk of bleeding precluded biopsy of the axillary arterial mass. He was followed for 2 weeks as an outpatient and was ultimately admitted to our facility after detailed examination.

The patient's clinical course is shown in Fig. 2. As mentioned above, although the clinical findings were atypical for sepsis and mycosis, we started antibiotics to target *Staphylococcus aureus* (cefazolin sodium 1 g/day) and began an

Table 1 Laboratory data of non-dialysis day on presentation

	Reference range		Reference range
<Complete blood count>		<Coagulation>	
White blood cell	12,150/ μ L	PT-INR	1.12
Neutrophils	91.0%	APTT	31.1 s
Red blood cell ($\times 10^4$)	262/ μ L	Fibrinogen	913 mg/dL
Hemoglobin	8.4 g/dL	FDP	12.3 μ g/mL
Platelets ($\times 10^4$)	20.1/ μ L	D-dimer	3.52 μ g/mL
<Serum biochemistry>		<Immunological study>	
Total protein	6.4 g/dL	C-reactive protein	9.13 mg/dL
Albumin	2.9 g/dL	Procalcitonin	0.6 ng/dL 0–0.1
Blood urea nitrogen	73.1 mg/dL	Soluble interleukin-2 receptor	1855 U/mL 144.5–518.0
Cr	8.6 mg/dL	Complement 3	109.4 mg/dL
Uric acid	6.1 mg/dL	Complement 4	47.8 mg/dL
Total bilirubin	0.3 mg/dL	Serum complement titer	51.4 U/mL
Aspartate aminotransferase	24 U/L	Immunoglobulin G	961.3 mg/dL
Alanine aminotransferase	23 U/L	ANA	Negative
Alkaline phosphatase	204 U/L	MPO-ANCA	< 1.0 U/mL
γ -Glutamyl transpeptidase	28 U/L	PR3-ANCA	< 1.0 U/mL
Lactate dehydrogenase	255 U/L	Aspergillus antigen	0.5 0–0.5
Total cholesterol	191 mg/dL	Candida antigen	Negative
LDL-cholesterol	108 mg/dL	Cryptococcus neoformans antigen	Negative
Sodium	139 mEq/L	Beta-D-glucan	8.11 Pg/mL 0–11.0
Potassium	4.3 mEq/L	MAC antibody	0.5 U/mL 0–0.7
Chloride	99 mEq/L	Quanti-FERON	Negative
Corrected calcium	9.4 mg/dL	Blood culture	Negative
Phosphate	2.8 mg/dL		

ANCA anti-nuclear antibody, APTT activated partial thrombin time, Cr creatinine, FDP fibrinogen degradation products, LDL low-density lipoprotein, MAC *Mycobacterium avium* complex, MPO myeloperoxidase, PR3 proteinase 3, PT-INR prothrombin time-international normalized ratio

Fig. 1 Contrast-enhanced computed tomographic (CT) imaging of the left axillary arterial mass (a), plain CT imaging of the multiple lung tumors (b)

Fig. 2 Patient's clinical course. CEZ cefazolin sodium, CRP C-reactive protein, L-AMB liposomal amphotericin B, MCFG micafungin sodium, VCM vancomycin hydrochloride

intravenous antifungal agent (micafungin sodium 100 mg/day) for possible bacterial or fungal arterial aneurysm and septic pulmonary embolism. Because he was unresponsive to treatment, we changed the regimen to vancomycin hydrochloride (0.5 g every HD day following an initial dose of 1.5 g) and liposomal amphotericin B (2.5 mg/kg/day) to target methicillin-resistant *Staphylococcus aureus*, aspergillosis, or disseminated cryptococcosis. Bronchoalveolar

lavage and transbronchial lung biopsy were performed on hospital day 2. However, neither cytological nor histological diagnosis revealed the final diagnosis of malignancy or infection. On hospital day 3, he showed exacerbation of pain and disturbances in consciousness with a blood pressure of 94/56 mmHg, heart rate of 116 beats per minute, and progression of anemia (hemoglobin 7.6 g/dL). Follow-up CT revealed increased tumor size (93 mm long $\times$ 63 mm wide in

diastole) and hematoma (Fig. 2). We, therefore, performed emergency surgery to resect the left axillary mass diagnosing hemorrhagic shock. Under systemic anesthesia, a sheath was inserted into the femoral artery. We inserted a pigtail catheter with guidewire to the origin of the left subclavian artery. An indwelling angiographic catheter was then placed at the origin of the left subclavian artery and contrast administered to confirm the hemodynamics around the mass. We were thereby able to detect the main axillary artery's occlusion and collateral circulation forward to the distal artery (Fig. 3a). Because of the presence of the collateral artery, we retracted and resected the left axillary tumor, assuming

that the resected mass did not contribute to distal perfusion. After resection of the tumor, there was no hemodynamic change in the contrast findings (Fig. 3b). His consciousness disorder had once improved after surgery and administration of red cells concentrates.

Macroscopic inspection of the resected specimen revealed breakdown of the vascular wall (Fig. 4a), and the lumen was filled with thrombus. Microscopic findings revealed vascular cellular atypia (Fig. 4b) and CD31, a vascular endothelial marker, was positive. The patient was diagnosed with angiosarcoma by histopathological examination on hospital day 15. His condition deteriorated gradually to Eastern

Fig. 3 Angiographic images before (a), after (b) the resection of the left axillary arterial tumor. **a** The tumor is indicated by the white dotted circle. Red arrows indicate the collateral artery. **b** The white arrow indicates that the collateral artery settled caudally after excision of the tumor

Fig. 4 Pathology and histopathology of the resected left axillary arterial tumor. **a** Macroscopic specimen (left panel) and cross sections (right panel) with red outlines indicating parts of the tumor; **b** hematoxylin–eosin staining of paraffin-embedded section. The vas-

cular wall has several slit-like lumens (left panel). Higher magnification shows dense cellularity with prominent atypia of cell nuclei and nucleoli (right panel)

Table 2 Characteristics of angiosarcoma from previous case reports and our patient in hemodialysis or post-renal transplant ($n = 29$)

Age (years)	55 ± 13	<Complains and symptoms>	
Sex (male)	25 (86)	<i>Pain</i>	19 (66)
Post-renal transplant	20 (69)	<i>Mass/swelling</i>	19 (66)
Immunosuppressive therapy	20 (69)	<i>Bleeding/subcutaneous hematoma</i>	3 (10)
Duration required diagnosis [week ($n = 7$)]	14 ± 13	<i>Cough/Dyspnea</i>	3 (10)
Survival duration [month ($n = 16$)]	7.1 ± 4.6	<i>Paresthesias</i>	1 (3)
<i>Nonfunctional AVF ($n = 20$)</i>	16 (80)	<Initial diagnosis> ($n = 22$)	
<Vascular access type>		Thrombosis	8 (36)
Brachio-cephalic AVF	16 (55)	<i>Infection</i>	7 (32)
Radio-cephalic AVF	11 (38)	<i>Arterial aneurysm</i>	2 (9)
AVG	1 (4)	<i>Abscess</i>	1 (5)
<Treatment> ($n = 21$)		<i>Skin disease</i>	1 (5)
<i>Resection</i>	20 (95)	<i>Sarcoma</i>	1 (5)
<i>Chemotherapy</i>	7 (33)	<i>Arteriovenous malformation</i>	1 (5)
<i>Radiotherapy</i>	6 (29)	<i>Angiosarcoma</i>	1 (5)

Data are expressed as mean ± standard deviation or number (percentage)

Italics text indicates characteristics that apply to our patient

AVF arteriovenous fistula, AVG arteriovenous graft

Cooperative Oncology Group Performance Status score 4, completely disabled (unable to manage any self-care, totally confined to a bed or chair); therefore, we could not administer chemotherapy. We consulted oncologists at other facilities, and they concurred with our assessment. Hence, we provided supportive care to him, not chemotherapy. Although he had no metastasis other than the lung, respiratory failure has progressed with metastatic lung tumors enlargement. On hospital day 25, he expired. Hemodialysis continued until just his death.

Discussion

We report the finding of an axillary arterial angiosarcoma in a nonfunctioning arteriovenous fistula limb of a patient undergoing HD. The disease was highly aggressive and the patient died only 6 weeks after first presentation.

Angiosarcoma is a subtype of soft-tissue sarcoma, representing 1% of all soft-tissue sarcomas. It comprises malignant endothelial cell tumors of vascular or lymphatic origin. It is aggressive and has a high rate of local recurrence and metastasis. It, therefore, has a generally poor prognosis, with overall survival ranging from 6 to 16 months [1]. The most common presenting symptoms are pain with or without formation of a mass, and the initial diagnosis is most often thrombosis of the fistula with a delay in correct diagnosis between 2 and 40 weeks [2]. Amputation is the most common treatment and, historically, angiosarcoma has a 5-year survival rate of 10–20% [4].

There have been several cases reported in the literature that describe the development of angiosarcoma at the site

of a nonfunctional AVF. Most of the patients with angiosarcoma-related HD or vascular access were status post-renal transplant or on long-term immunosuppressive therapy. With respect to AVF, altered lymphoid dynamics surrounding these sites mimics lymphedema and thus may contribute to angiosarcoma development, with previous reports suggesting that the altered regional lymphatic flow could also cause a localized immunosuppressive environment, further confounding this effect [5]. Implantable materials such as synthetic grafts or materials required for surgery such as gauze, sponge, and suture have also been assumed as causative factors of angiosarcoma [2]. Immunosuppression is a known risk factor for increased rates of all cancers [6]; therefore, at least long-term immunosuppressive therapy can contribute to the onset of angiosarcoma. Patients who are post-renal transplant may be on an immunosuppression regimen and have nonfunctional vascular access.

In the present case, the patient had taken corticosteroids because of a history of ulcerative colitis; however, he was not otherwise immunosuppressed. Angiosarcoma arose in his left nonfunctional AVF limb and it was possible that the above-mentioned mechanism contributed to the onset of the angiosarcoma.

Characteristics of 29 angiosarcoma case reports [4–21] including ours in HD or post-renal transplant patients are summarized in Table 2 (Italics text in Table 2 indicates items that apply to our case). There were many complaints of pain or a mass, as in our case. It is assumed that respiratory symptom such as cough that occurs in a minority of patients is because of lung metastasis. As with previous research in general, surgical treatment is often attempted and survival duration is poor (mean about 7 months). To be noted, it is

extremely rare that we can diagnose angiosarcoma initially; it takes an average of 14 weeks to diagnose correctly.

Regarding multiple lung tumors, the possibility of infectious disease such as septic pulmonary embolism cannot be completely excluded. Finally, we ruled out septic embolism with resistant to antibiotics and negative blood culture. It is unknown whether angiosarcoma in hemodialysis or post-renal transplant shows elevated inflammatory state as our case. To the best of our knowledge, one case report shows a mild increase in CRP (0.77 mg/dL) [21]. The autopsy has not been performed; therefore, the actual cause of death or origin of the lung tumors is unknown. This is one of our limitations in the present case report.

In summary, the present case emphasizes the importance of including angiosarcoma in the differential diagnosis for upper extremity pain in patients undergoing HD. Patients with angiosarcoma typically takes a long time to be diagnosed. Angiosarcoma is a rare but aggressive malignancy and has poor survivability; therefore, early diagnosis is important.

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Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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